UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/648,361	08/27/2003	Mart Saarma	0933-0210P	3435

2292 7590 12/30/2005

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/648,361	SAARMA ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 8-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 August 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to a response to a restriction requirement filed 10/13/05. Claims 1-26 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group II (claim 7) in the reply filed on 10/13/05 is acknowledged. The traversal is on the ground(s) that if the MANF2 polypeptide were novel, any means of making or using the polypeptide would be novel. Thus applicants request, should the polypeptide be found allowable, rejoinder of all process claims with the product claim and suggest that a search of all classes/subclasses would then not be necessary. Furthermore, applicants traverse the distinction between Groups I-XII. Specifically, applicants state that that a distinction between Group II and XII does not mean there is a distinction between Group I and II and Group I and XII. Finally, applicants argue that reconsideration of Groups I, II (sic), III and XIII under MPEP 806.05(d) is requested.

This is not found persuasive because of the following reasons. Group II has been elected and, as indicated in the office action mailed 9/23/05, Group II is related as product and process of using with Groups IV, VIII and XII and as product and process of making with Group III. In the instant case, the criteria for establishing that the inventions are distinct and can support separate patents have been set forth and met in the office action mailed 9/23/05 (see MPEP 806.05 (h)). As the inventions are distinct, the restriction requirement is still deemed proper. As to applicants request for rejoinder, the office action mailed 9/23/05 (page 7) sets forth guidance as related product and process claims. Briefly, rejoinder practice states, "Until an elected

product claim is found allowable, an otherwise proper restriction between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined". With regard to a search requirement and distinctness of Groups I-XII especially should the MANF2 polypeptide be found allowable, separate classification is but one component to consider when considering search burden. The MPEP teaches "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That prima facie showing may be rebutted by appropriate showings or evidence by the applicant" (see MPEP 803)." In the instants case, the inventions of Groups I-XII have a separate status in the art as shown by their different classifications and their recognized divergent subject matter. Furthermore, the searches required for the different groups are not coextensive.

Applicants have traversed the distinctions made between Groups I-XII. However, applicants have only argued that the distinction between Group II and XII should not be used to mean there is a distinction between Groups I and II and Groups I and XII. This response will be drawn to these remarks as applicants did not distinctly and specifically point out any other supposed errors. The distinction between Groups I and II and Groups I and XII have not been based upon the distinction between Group II and XII but have rather been separately set forth in the restriction requirement on page 4 paragraph 3 and page 5, paragraph 2 respectively in the restriction requirement mailed 9/23/05 and have not relied upon the distinction between Group I and XII. Finally, Groups I, II (sic), III and XII have not been labeled as subcombinations. On page 4 of the restriction requirement mailed 9/23/05, only Groups I and II have been indicated as

being subcombinations. Specifically, the invention of Group V is a combination made up of the subcombinations of Groups I and II, which is governed by MPEP 806.05(c). MPEP 806.05(d) is drawn to subcombinations usable together in a combination, which does not adequately represent the relationship between Groups V versus I and II.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

An IDS filed 2/9/04 has been identified and the documents considered. Documents listed that have not been located have not been considered and have been crossed out. If applicants want the items listed in the IDS filed 2/9/04 to be considered, new copies of the articles should be sent, accompanied by a new Form 1449. The signed and initialed PTO Form 1449 has been mailed with this action.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, the letter stating that the contents of the sequence listing and the CRF are the same must state that there is no new matter by the submission of the sequence listing and CRF. A new

sequence listing, CRF and letter stating that there is no new matter and that the contents of the sequence listing and CRF are the same is required.

Drawings

Figure 6 is objected to under 37 CFR 1.83(a) because it fails to show any details as described in the specification. Specifically, figure 6 is a photograph of a Western Blot. However, the details are indiscernible as the image is too dark. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

The title of the invention, *Novel neurotrophic factor protein and use thereof*, is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The use of novel in the title is objected to as inventions before the US Patent and Trademark Office are presumed to be novel.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 6, line 11 and page 20, line 12. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

On page 11, table A, MANF is misspelled as MAMF in the upper and lower table. On page 10, line 17 a space is missing between the words "Cos-7" and :cells".

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 7 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or well-established asserted utility or a well-established utility.

Claim 7 is drawn to an isolated MANF2 polypeptide comprising the amino acid of SEQ ID NO:2 of figure 7. Applicants teach that MANF2 was isolated based upon sequence homology to MANF1, which has *in vitro* properties that suggest it could be used for the treatment of Parkinson's disease and possibly other neurodegenerative diseases. MANF2 was cloned and purified from mouse and human cDNA libraries and found to encode 187 amino acids and to have about 80% identity between the mouse and human cDNA. MANF2 expression levels were assessed in multiple tissues. Based solely on the above observations, applicants have argued that MANF2 agonists can be used to stimulate proliferation, growth, survival, differentiation, metabolism or regeneration of MANF2 receptor containing cells. Hence MANF2 is said to be useful for development of a range of therapeutics and diagnostics fot the treatment and diagnosis of MANF2 dependent conditions (see e.g. page 1, paragraph 4). Specifically, MANF2 is said to be useful for *ex vivo* or *in vivo* administration to treat preferably neurological disorder preferably central nervous system disorders, Parkinson's disease, Alzheimer's disease (see e.g. page 43, paragraph 2) and especially peripheral neuropathy (see e.g. page 44, paragraph 2). As well,

MANF2 is proposed to be used as an effector of primary and central neurons and for purification of a receptor that binds to MANF2.

For "specific utility", the invention must have a utility specific to the subject matter claimed in contrast with a general utility that would be applicable to the broad class of the invention. According to 35 U.S.C. 101, a specific utility is not a list of potential applications for which the broad class of the invention would also have utility. Applicants' disclosure is to properties that are generic to essentially any protein. For example, applicants disclose that MANF2 may be useful for development of therapeutics and diagnosis of MANF2-dependent conditions. However, MANF2-dependent conditions are unspecified and undocumented. To be specific, the application must teach the skilled artisan in specific terms specific biological activities, and reasonably correlate that activity to a disease condition.

For "substantial utility", the invention must define a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. As well, the disclosure proposes use of MANF2 to act as an effector of primary or central neurons. The instant claims propose a function for the MANF2 that would require basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved. For example, the identification of MANF2-dependent conditions would be required prior to administration of MANF2 as a treatment or to diagnose such conditions as these are unspecified diseases or conditions. The ability of MANF2 to act as an effector of primary or central neurons would require basic research to determine this function. Furthermore, the specification proposes using MANF2 to identify MANF2 receptors. A "substantial utility" has not been confirmed for either

MANF2 or MANF2 receptors. Therefore, the proposed methods identify a material that itself has no disclosed specific and/or substantial utility. Applying these asserted utilities to a real-world problem requires that some specific useful feature of the polypeptide is known.

Finally, the invention lacks "well-established utility" in that the disclosure provides no specific teaching of the functional properties of the claimed polypeptide. Applicants have derived the function of MANF2 based upon its similarity to MANF1 and its tissue distribution. The ability to determine *a priori* the function of a protein based upon primary amino acid sequence or homology is poorly established in the art. In fact, Smith and Zhang teach that standard tools for assigning probable function to new sequences when recognizable homologs exist are problematic due to outright errors and inconsistencies. Smith and Zhang teach of numerous cases in which proteins of very different current functions are homologous yet share no common function (see e.g. page 1222, col 3, paragraph 2). Tseng and Liang further this by teaching that global protein sequence and structure similarity are often unreliable for function prediction as functional domains are subject to evolutionary pressure that is different than other residues. Simply comparing functions between two proteins does not take into account that homologs can and do have different molecular and cellular functions. Hence the practice of assigning function based upon homology is highly unpredictable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention recites an isolated MANF2 polypeptide comprising the amino acid of SEQ ID NO:2 of figure 7. The invention utilizes disciplines of molecular biology and cell biology.

2) **Scope of the invention**. The claims are drawn to the sequence of SEQ ID NO:2, MANF2, which is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

3) **Number of working examples and guidance**. MANF1 demonstrated an *in vitro* ability to protect the survival of embryonic mesencephalic dopaminergic neurons. Applicants teach that MANF2 was isolated based upon sequence homology to MANF1. MANF2 is expressed in all tissues analyzed by predominately in neurons, the heart, kidney, liver, skeletal muscle, prostate, thymus and regions of the brain. Based solely on the above observations, applicants have argued that MANF2 agonists can be used to stimulate proliferation, growth, survival, differentiation, metabolism or regeneration of MANF2 receptor containing cells. Hence MANF2 is said to be useful development of a range of therapeutics and diagnostics useful in the treatment of MANF2 dependent conditions (see e.g. page 1, paragraph 4). Specifically, MANF2 is said to be useful for *ex vivo* or *in vivo* administration to treat preferably neurological disorder preferably central nervous system disorders, Parkinson's disease, Alzheimer's disease (see e.g. page 43, paragraph 2) and especially peripheral neuropathy (see e.g. page 44, paragraph 2). As well, MANF2 is proposed to be used as an effector of primary and central neurons and for purification of a receptor that binds to MANF2.

4) **State of Art**. The proposed uses for MANF2 are generic to the broad class of proteins and have no specific and substantial or well-established utility. Applicants propose that MANF2 can be used therapeutically and as a diagnostic in the treatment of MANF2 dependent conditions, as an effector of primary and central neurons and as a means to identify MANF2 receptors. Yet, the function of MANF2 has not been established therefore this is not a substantial real world utility because it would require additional experimentation to reasonably confirm. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. The instant application proposes a function for

MANF2 that would require basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved. While applicants state MANF2 may be useful for development of therapeutics and diagnosis of MANF2-dependent conditions. However, MANF2-dependent conditions are unspecified and undocumented. This activity is proposed based upon the homology with MANF1. Furthermore, applicants propose use of MANF2 to isolate MANF2 receptors. However, these uses do not provide a "specific utility". For a "specific utility", the invention must have a utility specific to the subject matter claimed in contrast with a general utility that would be applicable to the broad class of the invention. To be specific, the application must teach the skilled artisan in specific terms specific biological activities, and reasonably correlate that activity to a disease condition. Therefore, and as related generation of transgenic animals, the proposed assays are a method of assaying for or identifying a material that itself has no specific and/or substantial utility. Applying these asserted utilities to a real-world problem requires that some specific useful feature of the nucleic acid molecule is known.

5) **Unpredictability of the art**. The art of predicting protein function based upon protein homology with other proteins or the ability to determine *a priori* the function of a protein based upon primary amino acid sequence or homology is poorly established in the art. In fact, Smith and Zhang teach that standard tools for assign probable function to new sequences when recognizable homologs exist is problematic due to outright errors and inconsistencies. Smith and Zhang teach of numerous cases in which proteins of very different current functions are homologous yet share no common function (see e.g. page 1222, col 3, paragraph 2). Tseng and Liang further this by teaching that global protein sequence and structure similarity are often

unreliable for function prediction as functional domains are subject to evolutionary pressure that is different than other residues. Simply comparing functions between two proteins does not take into account that homologs can and do have different molecular and cellular functions. Hence the practice of assigning function based upon homology is highly unpredictable.

6) **Summary**. The invention recites a sequence isolated by homology to MANF1 for which no specific or well-established utility is described.

Given the unpredictability of the art, the poorly developed state of the art with regard to predicting the structural/ functional characteristics of a protein from primary amino acid sequence alone, the lack of a specific and well-established utility and the lack of guidance as to disease or targets provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

December 22, 2005